CLINICAL IMPLICATIONS OF BASIC RESEARCH

The Clinical Implications of Basic Research *series has focused on highlighting laboratory research that could lead to advances in clinical therapeutics. However, the path between the laboratory and the bedside runs both ways: clinical observations often pose new questions for laboratory investigations that then lead back to the clinic. One of a series of occasional articles drawing attention to the bedside-to-bench flow of information is presented here, under the* Basic Implications of Clinical Observations *rubric. We hope our readers will enjoy these stories of discovery, and we invite them to submit their own examples of clinical findings that have led to insights in basic science.*

BASIC IMPLICATIONS OF CLINICAL OBSERVATIONS
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A Possible Role for Anti-idiotype Antibodies in SARS-CoV-2 Infection and Vaccination

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The pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is incompletely understood, with its effects on multiple organ systems[1] and the syndrome of "long Covid" occurring long after the resolution of infection.[2] The development of multiple efficacious vaccines has been critical in the control of the pandemic, but their efficacy has been limited by the appearance of viral variants, and the vaccines can be associated with rare off-target or toxic effects, including allergic reactions, myocarditis, and immune-mediated thrombosis and thrombocytopenia in some healthy adults. Many of these phenomena are likely to be immune-mediated.[3] How can we understand this diversity in immune responses in different persons?

One way of thinking about the complexity of the immune response is through the lens of anti-idiotype immune responses. The Network Hypothesis, formulated in 1974 by Niels Jerne, described a mechanism by which the antibody responses to an antigen themselves induced downstream antibody responses against the antigen-specific antibody.[4] Every antibody that is induced and specific for an antigen (termed "Ab1" antibody) has immunogenic regions, particularly in their variable-region antigen-binding domains, that are unique as a result of genetic recombination of immunoglobulin variable, diversity, and joining (VDJ) genes; VDJ recombination results in new and therefore immunogenic amino acid sequences called idiotopes, which are then capable of inducing specific antibodies against Ab1 antibodies as a form of down-regulation. A similar paradigm has been proposed for T cells. However, these regulatory immune responses are also capable of doing much more. The paratopes, or antigen-binding domains, of some of the resulting anti-idiotype (or "Ab2") antibodies that are specific for Ab1 can structurally resemble that of the original antigens themselves. Thus, the Ab2 antigen-binding region can potentially represent an exact mirror image of the initial targeted antigen in the Ab1 response, and Ab2 antibodies have even been examined for potential use as a surrogate for the antigen in vaccine studies. However, as a result of this mimicry, Ab2 antibodies also have the potential to bind the same receptor that the original antigen was targeting (Fig. 1). Ab2 antibodies binding to the original receptor on normal cells therefore have the potential to mediate profound effects on the cell that could result in pathologic changes, particularly in the long term — long after the original antigen itself has disappeared.

This aspect of regulation of immune-cell responses was postulated by Plotz in 1983 as a possible cause of autoimmunity arising after viral infection[5] and has since been supported experimentally by direct transfer of anti-idiotype antibodies. Ab2 antibodies generated against the enterovirus coxsackievirus B3 in mice can bind myocyte antigens, resulting in autoimmune myocarditis,[6] and anti-idiotype responses can act as acetylcholine receptor agonists, leading to myasthenia gravis symptoms in rabbits.[7] In addition,

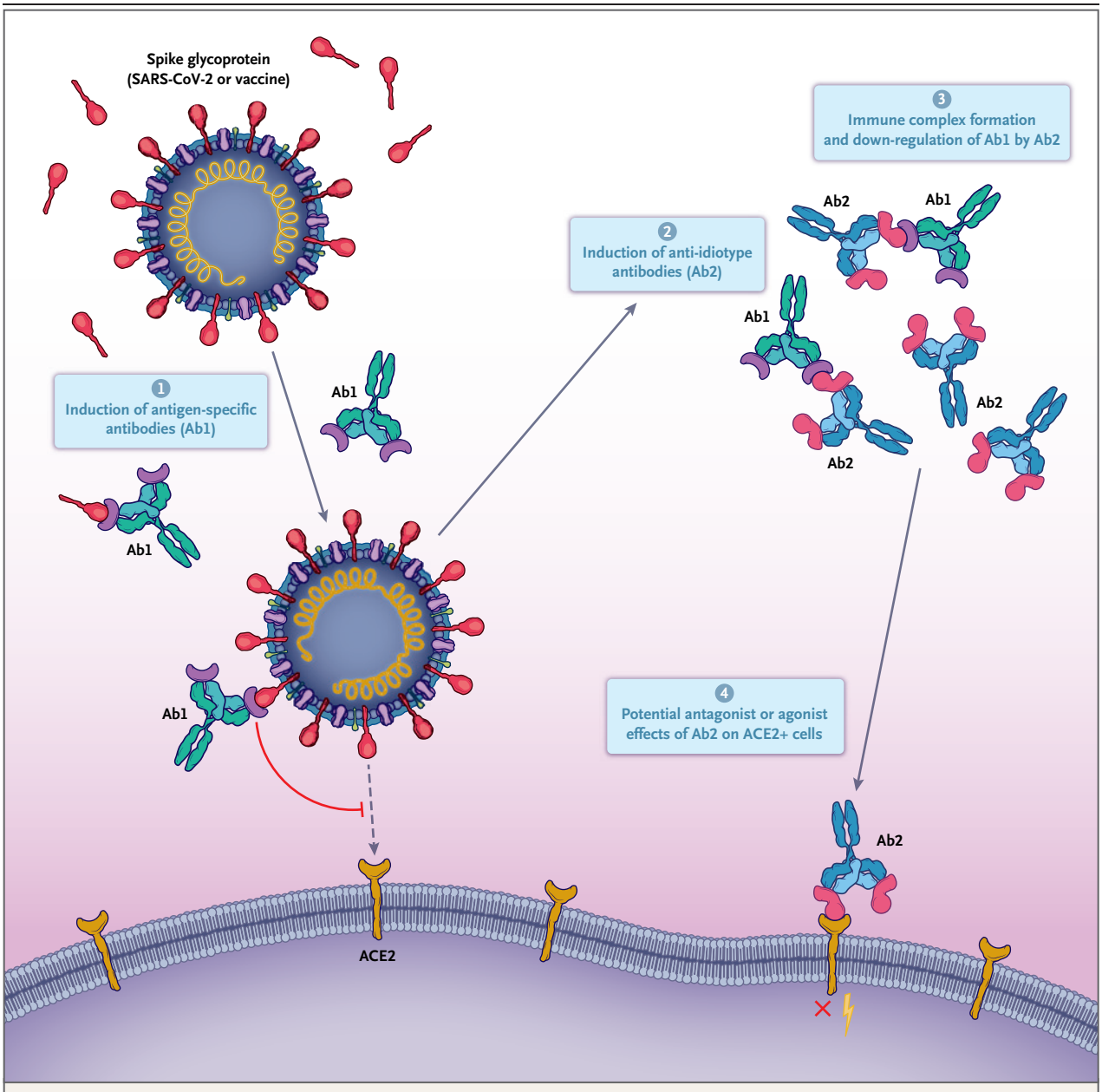

Figure 1. Anti-idiotype Antibodies and SARS-CoV-2.

Both severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the vaccines against it elicit antibodies to the spike protein that the virus uses to bind to the angiotensin-converting–enzyme 2 (ACE2) receptor on target cells. The receptor is widely expressed. These antibodies are called Ab1. The idiotype portions of Ab1 that bind and neutralize the spike protein have distinctive sequences in complementarity-determining region 3 (CDR3), and those antibody-binding regions can themselves elicit antibody responses called anti-idiotype (Ab2) antibodies as a means of down-regulation. Ab2 antibodies can act in several ways. They can bind to the protective neutralizing Ab1 antibody, resulting in immune-complex formation and clearance, thus impairing Ab1 efficacy. Some of the Ab2 binding regions, or paratopes, can also mirror the spike protein itself and bind to the same target as the spike protein, the ACE2 receptor. That binding could, in theory, exert several different — but not necessarily mutually exclusive — effects on the cell, depending on the nature of the Ab2 antibodies and the role of the receptors in the cell: for example, it could potentially block ACE2 function by competitively inhibiting normal ligand interactions. Alternatively, it could stimulate ACE2 function by triggering the receptor, affect expression of ACE2 after binding by down-regulating or internalizing ACE2, or, after binding the cells, induce a complement-mediated or immune-cell attack on ACE2-expressing cells.

by displaying the mirror image of the viral antigen, Ab2 alone can even mimic the deleterious effects of the virus particle itself, as has been shown with bovine viral diarrhea virus antigen.[8]

For SARS-CoV-2 infection, attention centers on the spike (S) protein and its critical use of the angiotensin-converting–enzyme 2 (ACE2) receptor to gain entry into the cell. Given its critical role in regulating angiotensin responses, many physiological effects can be influenced by ACE2 engagement.[9] The S protein itself has a direct effect on suppressing ACE2 signaling by a variety of mechanisms and can also directly trigger toll-like receptors and induce inflammatory cytokines.[10] Anti-idiotype responses may affect ACE2 function, resulting in similar effects. However, preclinical and clinical assessments of antibody responses to SARS-CoV-2 vaccines have focused solely on Ab1 responses and virus-neutralizing efficacy. The delineation of potential anti-idiotype responses has inherent difficulties because of the polyclonal nature of responses, dynamic kinetics, and the concurrent presence of both Ab1 and Ab2 antibodies. Furthermore, ACE2 expression within cells and tissues can be variable. The different vaccine constructs (RNA, DNA, adenoviral, and protein) are also likely to have differential effects on Ab2 induction or in the mediation of vaccine effects that differ from responses to infection. Some off-target effects may not be directly linked to Ab2 responses. The association of thrombotic events with some SARS-CoV-2 vaccines in young women and the etiologic role of anti–platelet factor 4–polyanion antibodies may be the result of the adenoviral vector. However, the reported occurrence of myocarditis after vaccine administration bears striking similarities to the myocarditis associated with Ab2 antibodies induced after some viral infections.[6] Ab2 antibodies could also mediate neurologic effects of SARS-CoV-2 infection or vaccines, given the expression of ACE2 on neuronal tissues, the specific neuropathologic effects of SARS-CoV-2 infection,[11] and the similarity of these effects to Ab2-mediated neurologic effects observed in other viral models.

It would therefore be prudent to fully characterize all antibody and T-cell responses to the virus and the vaccines, including Ab2 responses over time. Using huACE2 transgenic mice and crossing them with strains that are predisposed to autoimmunity or other human pathologic conditions can also provide important insights. An understanding of potential Ab2 responses may also provide insights into Ab1 maintenance and efficacy and into the application of antibody-based therapeutic agents. However, much more basic science research is needed to determine the potential role idiotype-based immunoregulation of both humoral and cell-mediated responses may play both in antiviral efficacy and in unwanted side effects of both SARS-CoV-2 infection and the vaccines that protect us from it.

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